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PRINCIPAL INVESTIGATOR:

Timothy M. Juergens, M.D.

CONTRACTING ORGANIZATION:

University of Wisconsin, Madison

Madison, WI 53715

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6. AUTHOR(S)
Timothy M Juergens MD
Giulio Tononi MD
Ruth Benca MD PhD
timothy.juergens@va.gov

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Wisconsin, Madison

21 N Park ST STE 6401
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14. ABSTRACT

The purpose of this study is to assess sleep and wake parameters in veterans of the first Gulf War who have fatigue and other symptoms compared with veterans who do not have fatigue utilizing novel assessment techniques including high density EEG. This research study is in the data collection phase. The most significant finding in this study during the research period is that the time course of slow wave activity (SWA) may be different in subjects endorsing fatigue compared to those who do not. Slow wave sleep is often thought to play a role in the recovery and restorative aspects of sleep.

15. SUBJECT TERMS
Dense array EEG, temperature, melatonin, vigilance

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Introduction

This research project assesses sleep and wake parameters in veterans of the first Gulf War who have fatigue and other symptoms compared to veterans who do not have fatigue. It utilizes novel assessment of brain waves with high density EEG, which allows for high spatial and temporal resolution to provide a window into how sleep is regulated at the global and local level. This will allow us to determine how specific sleep pattern activity is altered in veterans with fatigue. Beyond the typical overnight polysomnography, this assessment includes objective wave analysis of slow wave characteristics, origin and propagation. Circadian rhythm will also be assessed, including temperature and salivary melatonin measures, as well as salivary cortisol levels. Vigilance at various points will be tested with a psychomotor vigilance test, and there is an optional genetic testing part of the study to assess many polymorphisms that have been associated with other fatiguing conditions and symptoms.

Body

In the Statement of Work, we anticipated being in the recruitment and running subjects in the protocol phase, which is where we are currently. We have successfully completed 11 subjects in our study at this point, with one other mid-way and a few others being screened and scheduled. We are continuing to recruit subjects.

Data collected includes core, peripheral and distal body temperature, two nights of dense array EEG, multiple symptom scales involving fatigue, pain, and other symptoms, cortisol samples to be able to note diurnal changes, as well as morning cortisol rise from natural wake. We also have collected melatonin samples in a low light environment to be able to assess dim light melatonin onset. Psychomotor vigilance task (PVT) data has been collected at various points in the day in concert with subjective fatigue and sleepiness data.

All comments to findings and results as noted below are preliminary and based on a limited number of subjects. Therefore, there may be differences as more subjects are recruited and included.

Comparison of control versus fatigued group shows that on standard polysomnography there is not a significant difference when looking at two nights for each in the numbers of respiratory events or periodic limb movements (findings that are often the explanation of sleepiness/fatigue in the general population). This is anticipated, as we think there are other mechanisms behind fatigue in Gulf War illness. These are briefly presented in the tables below. Other typical parameters on the standard polysomnography (findings typically reported in a clinical overnight sleep study) also do not show differences. This may be due to low numbers currently, or may point towards the need for a more detailed/alternate approach to the assessment of the sleep quality (which was the premise for this study). Below are the tables for apnea hypopnea index and periodic limb movements of sleep.

t-Test: Two-Sample Assuming Unequal Variances on AHI (Apnea Hypopnea Index)

	Variable 1	*Variable 2*
Mean	3.475	2.4525
Variance	41.81357	19.15162
Observations	8	12
Hypothesized Mean Difference	0	
Df	11	

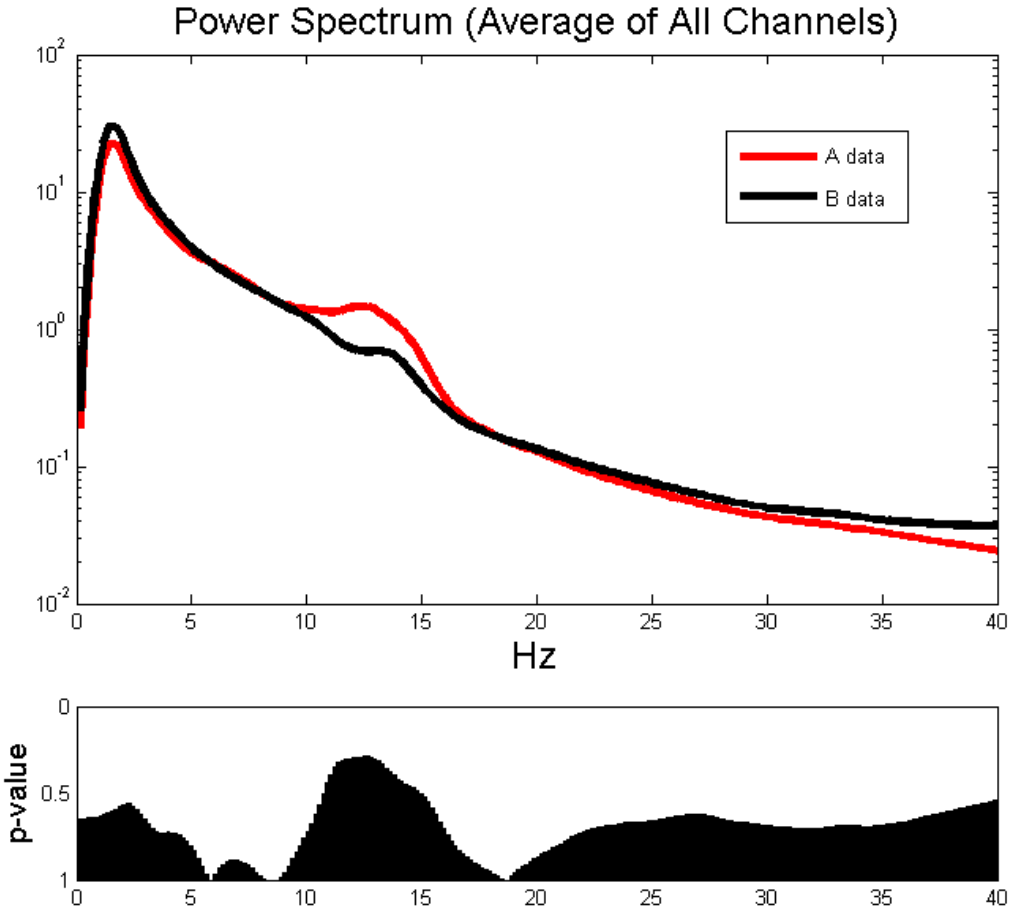
t Stat	0.391459
P(T<=t) one-tail	0.351467
t Critical one-tail	1.795885
P(T<=t) two-tail	0.702935
t Critical two-tail	2.200985

t-Test: Two-Sample Assuming Unequal Variances on Periodic Limb Movements

	Variable 1	*Variable 2*
Mean	5.0125	5.083333
Variance	163.4898	104.8252
Observations	8	12
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.01311	
P(T<=t) one-tail	0.494868	
t Critical one-tail	1.770933	
P(T<=t) two-tail	0.989735	
t Critical two-tail	2.160369	

The EEG data is in the processing/analysis stage. Detailed EEG analysis of our limited data includes overall topography data as well as power spectrum data averages. As we are still recruiting, data is preliminary and often not expected to reach statistical significance. However source analysis of our current subjects shows:

There is not a significant difference in the average of all channels for all frequency ranges. These will be further reported into the separate cycles across the night. There was a slight differences in the slow wave spectrum (1-4 Hz), again across the whole night with all channels, which was not significant at this point. There were also some non significant differences in the 10-15 cycles per second range (seen in following figure), which is the range of sleep spindle activity, which are characteristic aspects that define clinical stage 2 sleep and are generated by thalamic and corticothalamic activity.



In looking at all NREM sleep through the night, while no channels are significantly different in absolute SWA, when overall SWA is taken into account comparing across all night, the fatigue group has relatively more slow wave activity in the right tempoparietal channels as noted in the following figure.

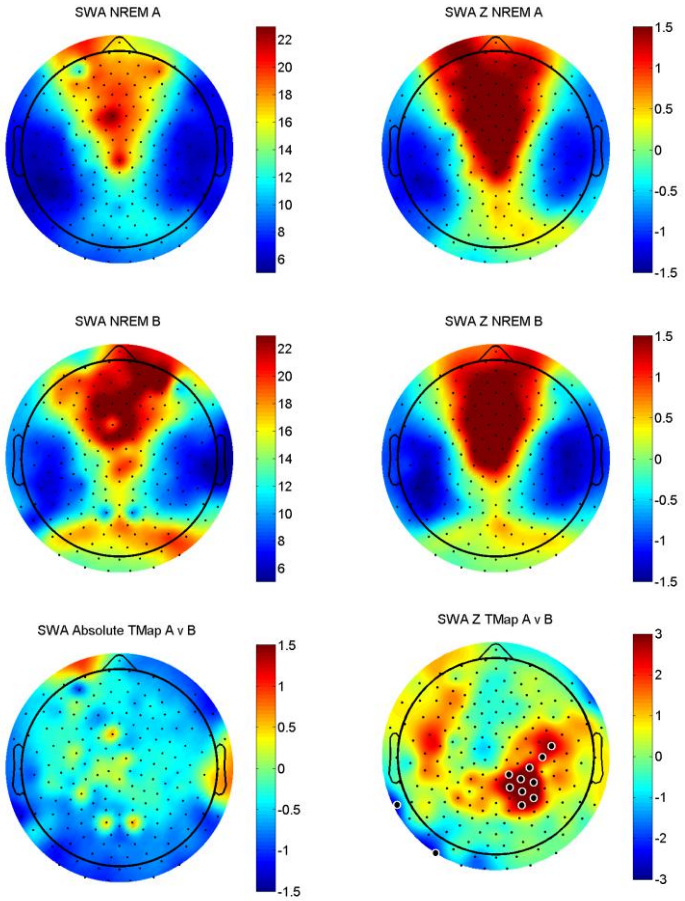


Figure : Absolute (left) SWA (1-4Hz) topography and spatially normalized (Z-score normalization, right) SWA topography for Group A (top row) and Group B (middle row). Uncorrected T-values (based on individual channel comparisons, bottom row) reveal that although there is no difference in absolute SWA, when overall SWA is taken in to account for each subject (normalized values, bottom right) Group A has relatively more SWA in a cluster of right temporoparietal channels. Significant channels ($p<.05$) are indicated as larger black circles outlined in white.

This is consistent across the first three NREM cycles (see figure below).

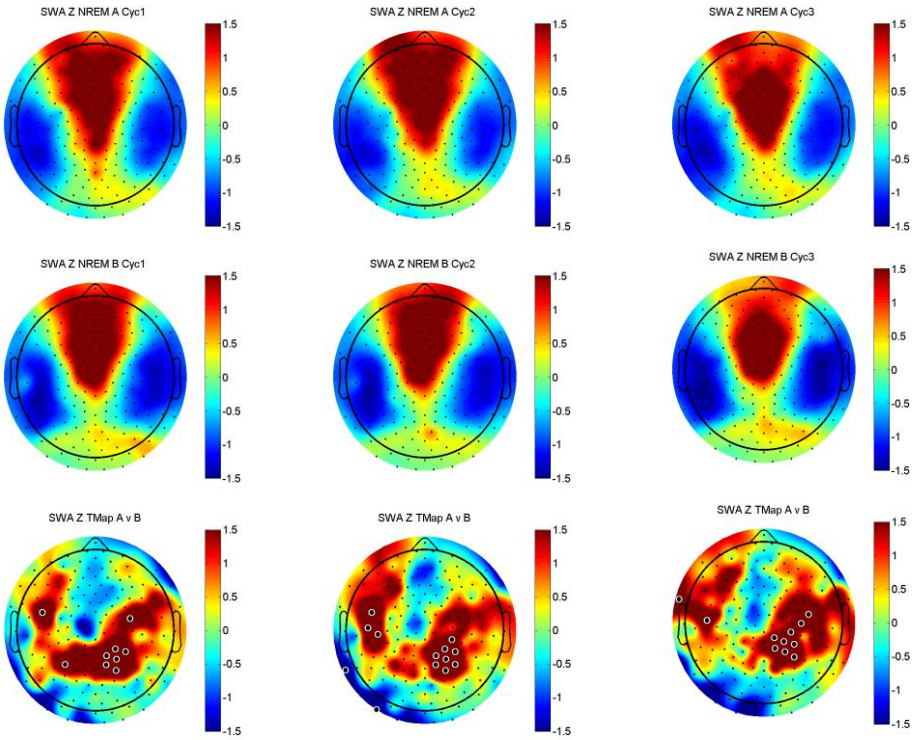


Figure : Comparisons of NREM cycles for Z-normalized values, shows that the relative local increase in the cluster of right temporoparietal channels is consistent across the first three NREM cycles (columns 1-3). Group A is top row, Group B is middle and uncorrected T-value maps are shown in the bottom row. Larger black circles outlined in white indicate significantly different channels $p < .05$. A few left frontotemporal channels are also different but are not necessarily consistent across cycles.

Additionally, the time course across cycles may be different . In literature, SWA has potential roles in recovery after a day of wake, and may impact fatigue as well as cognitive symptoms. This finding will be further assessed and pursued as additional data is collected.

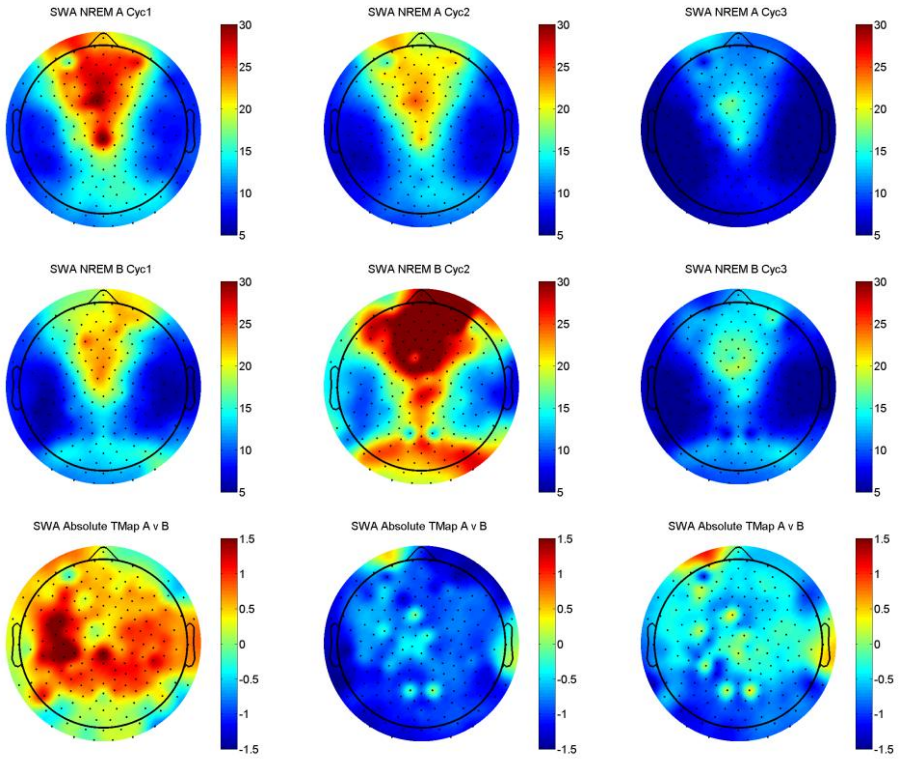
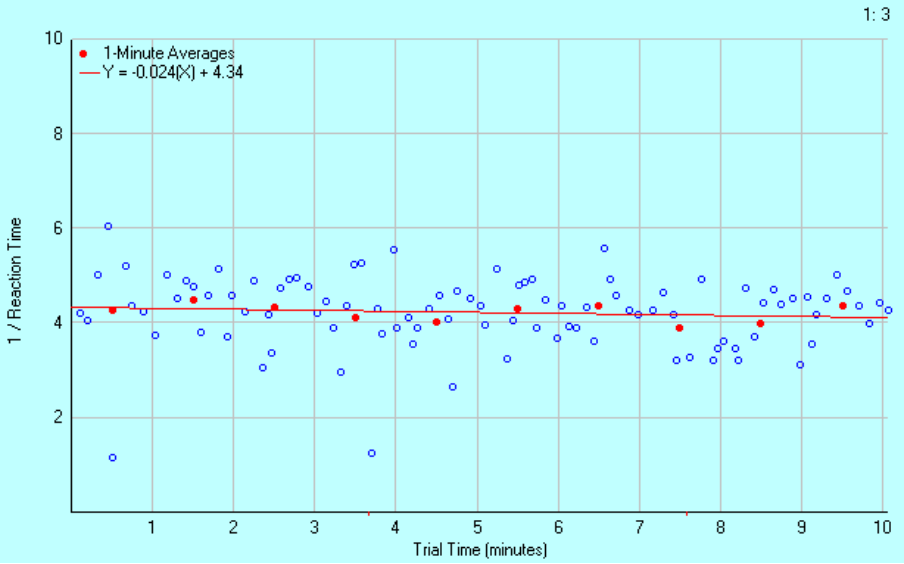
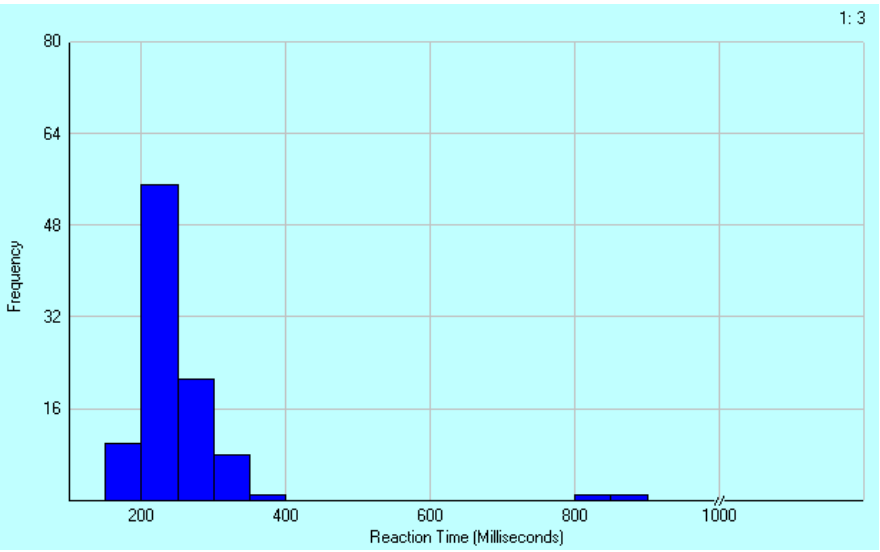


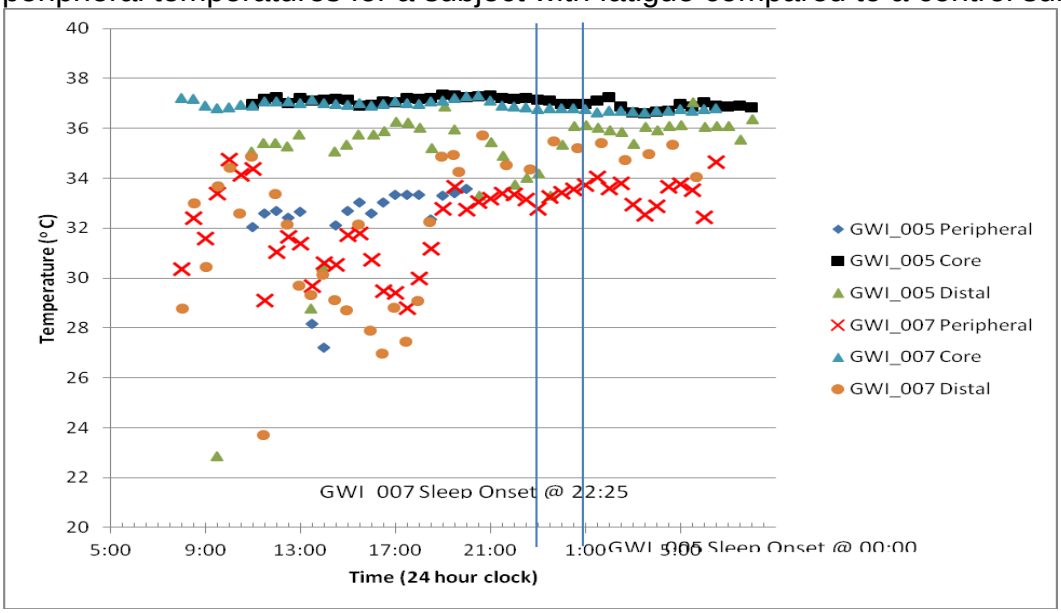
Figure : Comparisons of Absolute SWA across NREM cycles (columns) shows that no channels are significantly different (bottom row, t-values) when comparing Group A (top row) to Group B (middle row) but the timecourse across the cycles may be different between the two groups, as evidenced by the dissimilarity between the top and middle rows. Especially in NREM cycles 1 and 2.

Other data points assessed will now be reviewed.
PVT (psychomotor vigilance task) data is collected at multiple points in the study with subjective fatigue responses over a 10 minute duration. We will compare from various times, with levels of fatigue and between subjects when more data is available. Briefly, our current data indicates that when looking at all trials across the day and evening (5 in total per subject), there is in increased mean reaction time overall for subjects with fatigue compared to control subjects (so slower to respond to stimulus, less vigilant), as well as more lapses to respond, more total errors in the subjects with fatigue. The figure included below is for demonstration only of some of the responses on one PVT test on one subject.





Temperature findings are being processed. Below is a graph showing a curve for the core, distal and peripheral temperatures for a subject with fatigue compared to a control subject without fatigue.



Multiple scales including pain, sleepiness, fatigue, and quality of life are used in this study. Subjects with fatigue scored higher on the Multidimensional Fatigue Symptom Inventory-Short Form, but not on the Epworth Sleepiness Scale (ESS). This is consistent with what we anticipate, that the issue for these veterans is truly fatigue and feeling more run down and low energy, compared to feeling literally like one is going to fall asleep during day situations (reflected on the ESS).

t-Test: Two-Sample Assuming Unequal Variances on MFSI-SF (Multidimensional Fatigue Symptom Inventory-Short Form).

	Sleepy	*Control*
Mean	43	19.75
Variance	117	74.25
Observations	7	4
Hypothesized Mean Difference	0	
Df	8	
t Stat	3.914519	
P(T<=t) one-tail	0.002226	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.004453	
t Critical two-tail	2.306004	

t-Test: Two-Sample Assuming Unequal Variances on Epworth Sleepiness Scale (ESS)

	Sleepy	*Control*
Mean	9.714286	8.25
Variance	51.90476	28.25
Observations	7	4
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.384839	
P(T<=t) one-tail	0.355193	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.710386	
t Critical two-tail	2.306004	

Melatonin and cortisol samples have been collected for each subject. These are batched and will be processed together at a later date when samples from additional subjects have been collected.

Key Research Accomplishments

Recruiting
Initial collection of data
Data processing
Some data analysis

Reportable Outcomes

Reportable outcomes have not yet occurred. We are currently early in the data collection phase.

Conclusion

At this stage of data collection, substantial conclusions would be premature. However, we have shown that subjects who served in the first Gulf War who have extreme fatigue express that fatigue despite sufficient night sleep time, and time similar to those who do not have fatigue. However, the topographic slow wave activity shows that while all NREM average amounts of absolute SWA are not different, there may be some topographic areas of differences. Also, the time course across the cycles with regards to SWA may be different. Further EEG analysis of other parameters in sleep is also anticipated.

This finding offers some potential areas of future targeted treatments. Other potential contributors will continue to be assessed when they are analyzed (batched), such as melatonin and cortisol.

References

none

Appendices

none